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The inheritance pattern of dysplastic naevi in families of dysplastic naevus patients

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Dysplastic naevi (DN) are the major precursor lesions of malignant melanoma, yet the presumed mode of inheritance or genetic aetiology of DN remains controversial. The inheritance pattern of DN in families from a randomly selected population of 26 dysplastic naevus patients was investigated by estimating the segregation ratio in families ascertained through an offspring with DN (incomplete ascertainment). For families ascertained through a parent with DN (complete ascertainment) the transmission pattern was examined by comparing the observed number of affected offspring to the expected number using a χ^2 goodness-of-fit test. Results from the χ^2 tests and the estimated segregation ratio of 0.52 (95% confidence interval: 0.31, 0.73) suggest that the inheritance pattern for dysplastic naevi in these families is consistent with autosomal dominant transmission, although the present study was limited because of a small sample size. The findings, therefore, need to be confirmed by a much larger study that is able to test more rigorously specific genetic hypotheses.

Key words: Dysplastic naevi, genetics, inheritance, melanoma.

Introduction

Dysplastic naevi (DN) are the major precursor lesions for both familial and sporadic cutaneous malignant melanoma (CMM).[1–4] In familial melanoma kindreds, the presumed mode of inheritance or genetic aetiology of DN remains controversial.[5–10] Dysplastic naevi associated with familial melanoma are clinically and histologically indistinguishable from other dysplastic naevi. The prototypic dysplastic naevus is larger than a common acquired naevus, has a macular component with or without a papular component, and is irregular and indistinct in both outline and colour. Tan and brown hues predominate, while areas of erythema and blue/black speckles may develop in some lesions. In patients with multiple DN, there is often striking variability from one lesion to another.[11] Understanding the inheritance pattern of DN will help determine an individual's probability of having DN and possibly also his/her risk for developing malignant melanoma. This study was undertaken to examine the segregation pattern of DN in families from a randomly selected population of DN patients.

To test a particular genetic hypothesis in experimental animals investigators make controlled crosses and directly study the offspring of these controlled matings. We cannot make controlled crosses in humans and therefore can only test genetic hypotheses indirectly by fitting probability models to family data. We compare the observed proportion of affected individuals with the expected proportion under particular genetic models.[12] The purpose of this procedure, called segregation analysis, is to study how a disease or trait is transmitted from one generation to the next. For example, if a disorder is inherited as an autosomal dominant, one expects half the offspring of an affected individual to be affected. For an autosomal recessive disorder in which both parents are heterozygous (that is, they are carriers of the gene for the trait but do not express the trait), one expects on average that one-quarter of their offspring will be affected. In segregation analysis, therefore, we try to test statistically whether a disease conforms to the expected segregation ratio for a presumed mode of inheritance.[13] Consistency with the genetic model is a necessary but not sufficient criterion to identify a genetic aetiology.

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Subjects and methods

The patients for the present study were originally recruited in 1980–81 and evaluated for the presence of DN during a routine dermatology examination in a general dermatology practice.[14] At the time of the original identification of patients, the dermatologist evaluating the patients was establishing a new practice and was not known by the community to be interested in pigmented lesions. The presenting diagnoses of the patients, therefore, were typical of a general dermatology practice. A random sample of 26 of the patients reported in 1984 as having histologically confirmed DN were chosen to be the cases in a case-control study which examined the relationship between the total number of naevi and the presence of DN, and explored the percentage of DN patients with a family history of DN or CMM.[15] These same cases were used in the present study to evaluate the segregation pattern of DN.

All potential study subjects were contacted by telephone and asked to participate in the study. Participation included full body skin examination, biopsy of lesions suspicious of DN, completion of a brief self-administered questionnaire, permission to review medical records and permission to contact first-degree relatives (parents, siblings and children of the subjects) to ask them to participate. Participation was restricted such that individuals had to have reached their teens to enter the study. No age restrictions were imposed on parents and it is, therefore, possible that DN in some older individuals may have differentiated beyond recognition. Eighty-four per cent of the individuals contacted agreed to participate in the study. Participants and non-participants were similar in age, gender and race. All living parents, siblings and children were contacted if possible. Relatives living within 100 miles of Napa, CA, USA were asked to come to Napa for examination. Relatives living outside that radius who were willing to participate were evaluated in Bethesda, MD, USA ($n = 16$).

All study subjects underwent a full skin examination. Data were recorded on a standardized form. If a pigmented lesion was suspicious for a dysplastic naevus, the study subject was offered excisional biopsy for histological confirmation. Clinical characteristics of excised naevi were also recorded in a standard fashion. Clinical diagnosis of a dysplastic naevus for purposes of this study required a size greater than 4 mm, presence of a macular component, variegation of colour, and an irregular or indistinct border. Diagnosis of clinical DN required an individual having one or more DN. Some clinically diagnosed DN had been removed during the interval between original identification in 1980–81 and initiation of the follow-up study several years later.[15] Attempts were made to obtain pathology slides from all previously excised naevi for histological review. Individuals were classified as affected with DN if they had both clinical and histological evidence of DN.

The histological diagnosis of dysplastic naevus was made on the basis of architectural and cytological changes. The architectural changes included extension of the junctional component beyond a central dermal naevus, downgrowth and cross-bridging of adjacent ridges, often with fibroplasia within the papillary dermis and perivascular lymphocytes within a prominent superficial plexus. The cytological changes allowed classification as low-grade dysplasia, with only occasional cells with cytological atypia (defined as enlarged and/or hyperchromatic nuclei, prominent nucleolus and/or nuclear pleomorphism), or severe dysplasia, defined as more extensive changes of atypia, including confluent areas of atypical cells, but without upward migration of intraepidermal melanocytes. Without histological confirmation of DN, individuals could not be considered affected. Of the 41 individuals who were clinically diagnosed as having DN, 40 also showed histological evidence of DN. The one individual who was not biopsied was designated unaffected for the analyses.

Statistical methods

For the DN data, two types of families were included—completely and incompletely ascertained families. Ascertainment consists of the identification or location of individuals for study and is considered to be 'complete' if selection of the family is through the affected parent and all offspring are analysed whether or not they are affected. Complete ascertainment is useful mainly for examining dominant or common traits.

By contrast, 'incomplete' ascertainment involves selection of a family through an affected child who is a proband (where a proband is defined as the individual(s) through whom the family is brought to clinical attention). Incomplete ascertainment is further categorized based on the relative probability of ascertaining an affected child. This probability, π, ranges from 0 to 1. When π equals 1, all affected individuals are probands. At the other extreme, when π approaches 0, there is only one proband per family. Finally, when $0 < \pi < 1$, there may be more than 1 proband in a family and different families may have different numbers of probands.[12]

Since incomplete ascertainment involves selection of families through affected children, it will produce a biased segregation ratio because: (i) families in which both parents are heterozygous but by chance produce no affected children will be missing from the sample and (ii) since it is usually not possible to find all cases of a disease in a specified population, the more affected children there are in a sibship, the more likely it is that the sibship will be brought to clinical attention. Because of these two types of bias, one must use corrections of the data to estimate more accurately the segregation ratio.[12]

Estimation of the segregation ratio for the incompletely ascertained families was accomplished using the 'singles' method[13]. This method was originally developed by Gart[16] and Li and Mantel[17] for situations in which all affected individuals were probands. Davie[18] extended this method to be valid for all types of ascertainment. The segregation ratio, p, is calculated from

$$p = \frac{(R - P_1)}{(T - P_1)} \qquad (1)$$

where R = number of affected individuals in all sibships, T = total number of individuals in all sibships, P_1 = number of families with only one proband. Since each family in this sample contained only one proband, P_1 equals the number of sibships. The variance for the segregation ratio is:

$$p(1 - p)/(T - P_1) \qquad (2)$$

As examples, for a trait which behaves in a completely autosomal recessive manner, $p = 0.25$. If the trait is autosomal dominant, then the expected segregation ratio for the offspring from matings between one affected and one unaffected parent is 0.50.

Initially, the segregation ratio was estimated using only those siblings who consented to be examined. That is, all individuals who were not examined, and whose DN status was thus undetermined, were excluded from the estimation procedure. Then, to determine the possible effects of the excluded siblings, an approximate value of p was obtained by first assuming that all these individuals were unaffected, and secondly assuming these individuals all had DN. This procedure will produce 'minimum' and 'maximum' values of p with the true value lying somewhere between the two extremes (or, more precisely, between the two most extreme confidence limits derived from the two procedures).

The second approach utilized the completely ascertained families, that is, the offspring of the probands. For completely ascertained families, the transmission pattern can be determined by comparing the observed number of affected offspring to the expected number under the hypothesis of a particular genetic model using a χ^2 goodness-of-fit test.[12] This type of analysis requires that the 'mating type' of couples producing offspring be specified. For this analysis, a single 'mating type' was observed, that in which the proband had DN and the spouse was not examined. We used estimates of DN prevalence in the general population to calculate the expected ratio of DN-affected to DN-unaffected offspring. We chose upper and lower limits of DN prevalence of 1/6 and 1/50, respectively,[14,19–21] and examined both autosomal dominant and autosomal recessive transmission using the χ^2 test.

Finally, to try to differentiate polygenic inheritance from Mendelian transmission, we compared the observed relative frequency (that is, the frequency of DN in siblings of probands divided by the DN frequency in the general population) to the expected values for autosomal dominant, autosomal recessive, and polygenic models. The expected relative frequencies in siblings are $1/2q$ for an autosomal dominant trait, $1/4q$ for an autosomal recessive trait, and $1/\sqrt{q}$ for a polygenic trait where q equals the frequency of the trait in the general population.[12]

Results

Overall, 58% of the identified case relatives were willing and able to participate in this study. Table 1 presents the distribution of case relatives participating by category of relationship to the proband: 55% of the probands' parents participated in the study, and 62% of the non-participants were dead at the time of the study. For siblings, 45% participated in the study while 25% of the non-participating siblings were deceased when the study began. Finally, 75% of the probands' offspring were willing and able to participate in the study. The one deceased offspring died from malignant melanoma.

Each family was classified as to how informative it was for segregation analysis. Sibships were uninformative if the proband was an only child ($n = 1$) or if no sibling agreed to participate in the study ($n = 12$). Thirteen out of 26 of the probands' sibships were

Table 1. Participating and non-participating relatives of probands

Relatives of probands	Participants	Non-participants* Unknown	Deceased
Parents	23	11	18
Siblings[1]	23	21	7
Offspring[2]	30	9	1

* Unknown = no clinical information available on the individual; deceased = the relative known to be deceased at the time of the study.
[1] Only siblings who were full siblings of the cases were included in the analysis. That is, half-siblings were excluded from the analysis.
[2] Sixteen of 26 probands had at least one offspring. Offspring of 14 of the probands provided information for this study.

informative for analysis. In the informative families, 82% of siblings agreed to participate and were examined clinically. Four of eight siblings who did not participate (50%) were deceased at the time of the study. For the analysis using the probands' offspring, 14 of 16 families in which the proband had children were informative. In these 14 families, 83% of the probands' offspring participated.

Three of the cases (all from multiplex DN families) had a first-degree relative with a history of melanoma. Two of the melanomas were diagnosed prior to the first examination of the proband, and one was diagnosed 2 years after initial examination of the proband. All three patients with melanoma also had DN. The risk of melanoma in these families appeared to be increased, but was not as high as among members of familial melanoma/DN (that is, D2) families.[4,22]

Analysis using incompletely ascertained families

Table 2 shows the distribution of siblings from the incompletely ascertained families. Using equations (1) and (2) and the informative families, the segregation ratio was estimated to be: $p = (25 - 13)/(36 - 13) = 0.52$ and $\mathrm{Var}(p) = (0.52)(1 - 0.52)/(36 - 13) = 0.011$ with a 95% confidence interval of (0.31, 0.73). This analysis excluded all unknowns and used only those siblings who were clinically evaluated.

We next estimated the segregation ratio incorporating the unknowns into the analysis. Assuming that none of the unknowns had DN led to a lower limit segregation ratio of $p_L = (25 - 13)/(36 + 8 - 13) = 0.39$. Second, assuming that all the unknowns had DN, the upper limit $p_U = ((25 - 13) + 8)/(36 + 8 - 13) = 0.65$. This produced an interval ranging from 0.39 to 0.65. As a more conservative approach, we used the extremes of the confidence limits for the upper and lower segregation ratios. This produced an interval of (0.22, 0.82) which no longer excludes the segregation ratio that would be expected if the trait segregated in an autosomal recessive fashion ($p = 0.25$).

Analysis using completely ascertained families

Table 3 presents the distribution of offspring for the completely ascertained families and Appendix I shows the expected number of affected and unaffected offspring for each of the four hypotheses tested. It was possible to reject autosomal recessive inheritance for both estimates of DN prevalence used (χ^2 (1 df) = 12.65 and χ^2 (1 df) = 75.36 for DN prevalences of 1/6 and 1/50, respectively). Tests of autosomal dominant inheritance could not be excluded for either the upper or lower limit estimate of DN prevalence (χ^2 (1 df) = 1.73 and χ^2 (1 df) = 3.14, respectively). The segregation pattern in the completely ascertained families is thus consistent with autosomal dominant inheritance.

Table 2. Dysplastic naevi (DN) in families of DN patients: distribution of siblings in incompletely ascertained families

Family number	No. in sibship		
	DN affected[a]	Total[b] (known)	DN-status[c] unknown
Informative families			
101	2	2	2
104	2	2	2
105	2	2	0
106	2	3	1
107	3	3	0
109	2	2	0
110	4	5	0
115	2	2	0
118	1	3	0
125	1	2	1
126	1	3	0
127	1	2	1
130	2	5	1
Total	25	36	8
Uninformative families			
102	1	1	2
108	1	1	1
110	1	1	0
112	1	1	1
114	1	1	2
119	1	1	1
120	1	1	2
121	1	1	1
122	1	1	1
123	1	1	2
124	1	1	3
129	1	1	2
131	1	1	1
Total (all families)	43	58	28

[a] DN-affected = number of siblings in each family with DN.
[b] Total (known) = number of siblings with known clinical type ie. DN or no DN.
[c] DN-status unknown = number of siblings in each family with unknown DN diagnosis.

Inheritance pattern

Table 4 presents an examination of autosomal recessive, autosomal dominant, and polygenic inheritance of DN for the upper and lower limits of DN prevalence in the general population. A comparison of the observed and expected relative frequencies of DN in siblings shows

Table 3. Distribution of proband's offspring in completely ascertained families. Mating type: dysplastic naevi (DN) affected by DN-status unknown

Family number	No. of offspring		
	DN affected	Total (known)	DN-status unknown
101	0	2	0
102	2	2	1
104	1	1	1
109	2	2	0
111	1	2	0
114	1	2	2
115	1	2	0
118	2	2	0
122	1	2	0
123	0	2	0
124	2	3	0
126	1	1	0
127	5	5	0
129	1	2	2
Total	20	30	6

that the data are more consistent with autosomal dominant inheritance than either autosomal recessive or polygenic inheritance. For a DN frequency of 0.02, both polygenic and autosomal recessive inheritance models could be excluded. For a more common DN frequency of 0.167, the observed data are consistent with both an autosomal dominant trait and a polygenic trait. Even when the heritability is allowed to vary and be less than 100%, the data are still more consistent with an autosomal dominant trait than either a polygenic or autosomal recessive trait.[23]

Discussion

The results from the present investigation indicate that the segregation pattern of DN in the families of these randomly selected DN cases is consistent with autosomal dominant transmission ($p = 0.50$). For the incompletely ascertained families (excluding unknowns), a segregation ratio of 0.52 (95% CI: 0.31, 0.73) was estimated. Incorporating unknowns into the analysis produced a segregation ratio interval of (0.39, 0.65) using the point estimates and (0.22, 0.82) using the extremes of the confidence limits for the upper and lower segregation ratios. Since the segregation ratio for an autosomal dominant trait is 0.50, these results are consistent with autosomal dominant transmission. However, if the extremes of the confidence limits for the upper and lower segregation ratios are used, the segregation ratio for an autosomal recessive trait ($p = 0.25$) cannot be excluded. For the completely ascertained families, we could not reject hypotheses of autosomal dominant transmission for the upper and lower limit estimates of DN prevalence, whereas the hypotheses of autosomal recessive inheritance were both rejected. Finally, a crude assessment to differentiate polygenic transmission from autosomal dominant transmission revealed the data to be more consistent with autosomal dominant inheritance. For a lower limit of DN frequency, polygenic inheritance could be excluded. For an upper limit of DN prevalence, both autosomal dominant and polygenic inheritance were consistent with the observed data.

The present study raises several potential concerns. First, the analysis is based on an extremely small number of families (13 informative incompletely ascertained families, 14 completely ascertained families). Although the probands (and their families) were randomly ascertained from a general dermatology practice, the possibility of bias has to be considered. The probands were not representative of the general population, but rather, were representative of the population of individuals who seek care from a dermatologist. As such, the probands probably had more moles than would be found in a random sample from the general population. Second, a large number of family members did not participate in the study (see Tables 1 and 2). Family members may have been more willing to participate if they thought they had suspicious-looking naevi or if a family member had malignant melanoma. We tried to examine the possible bias from the unknowns by first classifying them all as affected and then as unaffected and examining the range of the segregation ratio. If

Table 4. Examination of autosomal dominant (AD), autosomal recessive (AR) and polygenic inheritance of dysplastic naevi (DN)

Frequency of DN		Observed/Expected frequency (s/q)	Expected relative frequency of DN in siblings for		
General population (q)	Siblings of cases[a] (s)		AD trait ($1/2q$)	AR trait ($1/4q$)	Polygenic trait[b] ($1/\sqrt{q}$)
1/6 = 0.167	0.52	3.11	2.99	1.50	2.45
1/50 = 0.02	0.52	26.00	25.00	12.50	7.07

[a] Frequency is corrected for the ascertainment event.
[b] Assumes 100% heritability.

the uninformative families were also included in the estimation procedure, classifying all the unknowns as affected and then as unaffected, the segregation ratio interval would be (0.28, 0.75). These procedures did not alter the results indicating that in the unknowns the probability of having DN may not have differed from that of their participating relatives.

A third concern is whether DN/CMM and DN alone are genetically the same trait. Kraemer *et al.* have hypothesized that there are several forms of DN, both familial and nonfamilial, that occur with and without melanoma.[24] The frequencies of the various DN types in the general population have not been measured. Furthermore, the genetics of these different types of DN has not yet been evaluated. There is thus a possibility of misclassification; that is, the families in the present study could include individuals with different genetic disorders with possibly different inheritance patterns. Unfortunately, at present there is no way to distinguish, either clinically or histologically, the familial melanoma-associated DN, other familial DN, or sporadic DN. It is, however, possible to examine the families segregating both DN and melanoma and compare them to those families segregating DN alone. In the sample, three families had one case of melanoma diagnosed. Excluding these families from the analyses did not alter the results.

Given the limited sample size and the large number of uninformative families, it was not possible to test specific genetic hypotheses rigorously. Ideally, we would have liked to have been able to conduct complex segregation analysis using available methods (e.g. Pointer,[25,26] Sage[27]), and incorporate age-at-onset, incomplete penetrance and phenocopy information as well as relevant environmental exposure information into the analysis. Only a much larger study will permit such an evaluation.

Although it was not possible to incorporate formally age-dependent penetrance into the analyses, the minimum age for participation in the study was restricted to the teen years to minimize misclassification, because DN may not manifest itself until the teens. The youngest participant was 17 years of age. On the other hand, no upper age limit was imposed and it is possible that DN in some older individuals (age >60 years) may have differentiated beyond recognition. Although this is a potential concern, only 17% (four of 23) of the probands' siblings were older than 55 years and negative for DN. We therefore do not feel that this possible misclassification would substantially alter the results.

Finally, given the small sample size, there was concern about the power of the study. There may not have been sufficient power to detect a deviation from an hypothesis of autosomal dominant transmission. We estimated the power for the χ^2-goodness-of-fit test. There was 66% power to reject an hypothesis of autosomal dominant transmission and 99% power to reject an autosomal recessive inheritance model.[28]

In conclusion, in the present study we investigated the inheritance pattern of DN in a small randomly-selected population of probands and their families using relatively simple statistical methods. The results, though tentative, suggest that the segregation of dysplastic naevi is consistent with an autosomal dominant pattern. These findings need to be confirmed in a much larger study that is able to use stringent statistical methods to evaluate the inheritance pattern of DN.

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Appendix 1

The mating type—dysplastic naevi (DN) affected by DN-status unknown—is used to determine the expected segregation ratio for the completely ascertained families. See Table 3 for the distribution of proband's offspring in the completely ascertained families. Since all matings were DN affected by DN-status unknown matings, we used upper and lower limit estimates of DN prevalences from the general population (1/6, 1/50, respectively) to calculate the expected proportions of DN-affected to DN-unaffected offspring. The χ^2 tests are as follows.

A. DN prevalence = 1/6 = 0.167

1. Autosomal dominant (AD) model (gene frequency (A) of DN = 0.09)

MT[a]	Frequency of MT	Proportion of MT	Proportion of offspring (assuming AD model)		Expected no. of offspring (sample size = 30)	
			no DN	DN	no DN	DN
AA × AA	0.00007					
AA × Aa	0.0027	0.0515	0.0	1.0	0.0	1.54
AA × aa	0.0134					
Aa × Aa	0.0268	0.0853	0.25	0.75	0.64	1.92
Aa × aa	0.2713	0.8632	0.50	0.50	12.95	12.95
Total	0.6857				13.59	16.41

[a] MT = mating type

$$\chi^2 = \frac{(20 - 16.41)^2}{16.41} + \frac{(10 - 13.59)^2}{13.59} = 1.73$$

2. Autosomal recessive (AR) model (gene frequency (a) of DN = 0.41)

MT[a]	Frequency of MT	Proportion of MT	Proportion of offspring (assuming AR model)		Expected no. of offspring (sample size = 30)	
			no DN	DN	no DN	DN
aa × AA	0.1170	0.3801	1.0	0.0	11.40	0.0
aa × Aa	0.1626	0.5283	0.50	0.50	7.92	7.92
aa × aa	0.0282	0.0916	0.0	1.0	0.0	2.75
Total	0.3078				19.32	10.67

[a] MT = mating type

$$\chi^2 = \frac{(20 - 10.67)^2}{10.67} + \frac{(10 - 19.32)^2}{19.32} = 12.65$$

B. DN prevalence = 1/50 = 0.02

1. Autosomal dominant (AD) model (gene frequency (A) of DN = 0.01)

MT[a]	Frequency of MT	Proportion of MT	Proportion of offspring (assuming AD model)		Expected no. of offspring (sample size = 30)	
			no DN	DN	no DN	DN
AA × AA						
AA × Aa	0.0002	0.0051	0.0	1.0	0.0	0.15
AA × aa						
Aa × Aa	0.0004	0.0102	0.25	0.75	0.08	0.23
Aa × aa	0.0388	0.9848	0.50	0.50	14.77	14.77
Total	0.0394				14.85	15.15

[a] MT = mating type

$$\chi^2 = \frac{(20 - 15.15)^2}{15.15} + \frac{(10 - 14.85)^2}{14.85} = 3.14$$

2. Autosomal recessive (AR) model (gene frequency (a) of DN = 0.14)

MT[a]	Frequency of MT	Proportion of MT	Proportion of offspring (assuming AR model)		Expected no. of offspring (sample size = 30)	
			no DN	DN	no DN	DN
aa × AA	0.0290	0.7474	1.0	0.0	22.42	0.0
aa × Aa	0.0094	0.2423	0.50	0.50	3.63	3.63
aa × aa	0.0004	0.0103	0.0	1.0	0.0	0.31
Total	0.0388				26.05	3.94

[a] MT = mating type

$$\chi^2 = \frac{(20 - 3.94)^2}{3.94} + \frac{(10 - 26.05)^2}{26.05} = 75.35$$